REMARKS

Applicants respectfully request reconsideration of the Final Office Action mailed on August 12, 2009 and allowance of the claims.

The rejection states claims 15, 18, 20-22 and 27-30 are pending and claims 18, 28-29 are withdrawn from consideration pursuant to 37 C.F.R. 1.142(b) as being directed to non-elected subject matter.

Applicants thank the Examiner for the explanation regarding the status of claims 28-29 and 15-18 (a result of the restriction and election of species).

Claims 15, 20-22 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the compound (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid (compound of claim 18 and 27 and encompassed by the generic formula of claim 15), does not reasonably provide enablement for the use of the same. The rejection states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The rejection states that the arguments set forth at p 3-12 of the previous office action dated March 4, 2009 are incorporated by reference.

The rejection states that though it is noted that Applicant has *identified* his compound as an alpha-2-delta ligand for use in treating various disorders in which the alpha-2-delta receptor is implicated, the fact remains that the instant specification fails to present any evidence, either in the form of data or scientifically sound reasoning, that would support the conclusion that the instantly claimed compounds actually do function as alpha-2-delta ligands and, therefore, would be functional for the disclosed utilities. The rejection states that Applicant relies upon the mechanism of action (i.e., as an alpha-2-delta ligand) underlying the purported biological activity to establish that the claimed compound would have been useful for the treatment of the various disclosed disorders in which the alpha-2-delta receptor is involved. The rejection states that in other words, Applicant's disclosed utility rests upon both the correlation and nexus between the particular activity of the claimed compounds as alpha-2-delta ligands and a reasonable expectation of usefulness in treating the disclosed disorders related to dysfunctions of the alpha-2-delta receptor. The rejection states that however, the instant specification fails to provide any disclosure pertinent to this nexus between the compound and the disclosed utilities. The rejection states that though Applicant provides various compounds and methods of synthesizing each, it again remains that Applicant has failed to demonstrate that the instantly claimed compound actually functions to achieve the disclosed therapeutic interaction with the alpha-2-delta receptor such that one of skill in the art would have thereby recognized its efficacious use in treating anyone or more of the disclosed disease states.

The rejection also states that these facts coupled with the fact that the specification also fails to present either via a working (or even prophetic) example(s) or a clear, scientifically sound explanation as to what, in fact, enables the interaction with the alpha-2-delta receptor such that the skilled artisan would have been imbued with at least a reasonable expectation of predictability of action in treating the disclosed disorders by effecting this action using the compound instantly claimed clearly supports the conclusion of a lack of enabling direction provided in the instant specification as to how to use the instantly claimed compound. The rejection states that this is because, absent such guidance, the experimentation required to determine if the claimed compound actually functions in the alleged manner such that it would have been expected to actually be useful for the disclosed utilities would be clearly undue for the reasons already made of record in the previous Office Action, which will not be repeated herein so as not to burden the record.

The rejection states that Applicant's statement that Julien implicitly, if not explicitly, requires pharmaceutical data for all pharmaceutical compound claims is not a point well taken. The rejection states that Julien does not contain any statement, explicit or otherwise, directed to a need to provide pharmaceutical data for all pharmaceutical compound claims. The rejection states that Applicant's comment to this effect is, therefore, clearly misplaced. The rejection states that Julien was cited for its clear teaching of the requirement for specificity of receptor-drug binding such that the conformation of a chemical compound must be sufficiently tailored to the particular receptor binding site such that it is actually able to bind the receptor and exert its biological effect. The rejection states that the fact that Julien uses an example of amphetamine and methamphetamine to illustrate this principle, as well as the principle that receptor-drug interactions are highly specific and that seemingly simple or uncomplicated modifications to a compound result in drastically different levels of pharmacologic activity such that compounds that share significant homology would not necessarily be capable of binding the same receptor, is immaterial because Julien still, in its broadest teaching, clearly teaches and supports the asserted unpredictability of drug-receptor binding. The rejection states that moreover, Applicant's statement that this amphetamine/methamphetamine example of Julien supports the instant claims because it teaches that the two compounds have different levels of activity but are still active is also unpersuasive. The rejection states that while the two compounds may preserve some level of activity, the fact remains that, in order to be useful for, for example, treating a disease, the compound must exert at least a threshold level of activity that is potent enough to elicit a positive therapeutic response by the patient (i.e., treatment of the disease). The rejection states that without at least this threshold level of activity, the fact that a compound may retain some minimal level of biological activity does not remedy the fact that the compound does not have enough activity to be therapeutically useful for the disclosed utilities.

The rejection states that though Applicant contends that the specification amply enables the instant claims, the specification in its entirety has been fully and carefully considered, but again fails to establish that the instantly claimed compound actually functions in the manner disclosed (i.e., as an alpha-2-delta receptor ligand) such that it would have been reasonably expected to be useful for the disclosed utilities. The rejection states that while it is understood that Applicant has provided extensive disclosure of the alpha-2-delta receptor, what disorders are associated with dysfunctions of alpha-2-delta receptors, therapeutic dosages of the compounds, how the artisan can administer the disclosed compounds, etc., it is again reiterated that the missing nexus in the instant disclosure is that the instantly claimed compound can, in actuality, function as an alpha-2-delta ligand. The rejection states that these sections of the specification (in particular, para.[0116], which Applicant states provides test protocols for determining relative activity of the compounds, but does not, in fact, provide such disclosure regarding so-called "test protocols"), while noted, do not overcome the fact that the instantly claimed compound must still be enabled to function as an alpha-2-delta ligand, which, for the reasons supra, and those already of record, it is not.

Applicant traverses the 35 U.S.C. §112, first paragraph, rejection of the claims and respectfully requests that the Examiner withdraw the final rejection and allow the claims (as amended).

As an initial note Applicants direct the Examiner's attention to paragraph [0428; the paragraph immediately preceding the claims] and the biological activity data contained in that table. The biological activity data is associated with the assay described in paragraph [0132] of the specification. That assay provides the nexus between the compounds and alpha-2-delta. Applicant further specifically notes that Examples 10 and 11 (the data for which is provided in the Table) are encompassed by claim 15.

Applicants herein below repeat their previous response as it remains applicable notwithstanding the final rejection.

As an initial note Applicant submits that the instant claims are drawn to compounds and pharmaceutical compositions. Accordingly, the claims only need to be enabled for a single utility. Nor are Applicant's claims limited to the treatment of a particular species e.g., humans. In contrast, Applicant notes that the rejection refers to a plethora of utilities and impliedly relates to the treatment of humans.

It is well settled law that the burden is on the Examiner to provide evidence why assertions of utility should not be accepted. In the instant case the Examiner has merely made conclusory statements without sufficient supporting evidence why Applicant's assertions of activity should not be accepted as true. Without such supporting information, the rejection of the specification/claims under 35 U.S.C. §112 first paragraph for lack of enablement is contrary

to well established law. Ex parte Kenaga, 189 USPQ 61, 64 (P.T.O. Bd. App. 1974), quoting In re Marzocchi, 169 USPQ 367 at 370:

> "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back assertions of its own with acceptable evidence or reasoning which is in consistent with the contested statement."
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> The C.C.P.A. held in In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971),
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> "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

Id. at 369. The burden is on the Examiner to come forth with evidence to establish a prima facie case. No persuasive factual evidence has been presented to establish a prima facie case pertaining to §112, first paragraph. Therefore, the statements in the present application must be taken as the truth. In re Langor, supra at 297; In re Marzocchi, supra at 369. Thus, Applicants request that the §112 rejection be withdrawn.

This issue has been revisited in In re Brana 34 U.S.P.Q.2d 1437 (CAFC 1995). The court quotes the above quotation from In re Marzocchi and concludes;

> "From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Id. at 224, 169 U.S.P.Q. at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility."

In re Brana 34 U.S.P.Q.2d 1437, 1441 (CAFC 1995).

While the new rejection is lengthy, and its text differs somewhat from the earlier rejection, Applicants submit that the instant rejection repeats the conclusory nature of the previous rejection. Essentially the rejection states that Applicants have not provided any activity data for their compounds. Yet the rejection again fails to provide any evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. This clearly is not sufficient to shift the burden under the standard enunciated by the CAFC.

Applicants also note that the rejection has not stated that the Applicants asserted treatment of certain diseases e.g., pain is an "incredible utility". Thus, Applicants assertions of utility should be acknowledged absent sufficient specific evidence such as mandated by the above caselaw.

The main difference in the instant rejection in comparison to the previous rejection is the inclusion of a reference Julien ("Chapter 2: Pharmacodynamics: How Drugs Act", *A Primer of Drug Action* (Ninth Edition); Worth Publishers, 2001:37-57) with the suggestion that this

reference is sufficient evidence to shift the burden to Applicants to provide activity data. The rejection broadly refers to the publication and pharmaceutical research in general stating the "unpredictability of receptor-drug binding in that the interaction is highly specific and that seemingly simple or uncomplicated modifications to a compound result in drastically different levels of pharmacologic activity". First, this is a conclusory general statement that, implicitly, if not explicitly, requires pharmaceutical data for all pharmaceutical compound claims. Yet this is simply not the standard by which enablement is judged as is clearly evident from, for example, the cited caselaw and the thousands of pharmaceutical compound patents granted by the United States Patent Office. The above textbook does not "provide[s] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility". Clearly any such evidence must be more specific and relate to the instant claims. Second, even the general statement supports Applicant's position since it states "simple or uncomplicated modifications to a compound result in drastically different levels of pharmacological activity." Applicant submits that even "drastically different levels of pharmacological activity" support enablement as there is some level of activity.

In addition, the specific example referred to in the rejection (Chapter 7) relating to the psychostimulants amphetamine and methamphetamine also does not shift the burden to Applicants. In fact it supports Applicant's claims. The rejection admits that both compounds while differing in structure are active. Applicant submits that some level of activity is sufficient evidence of utility. Again, the example simply does not support the rejection since the rejection admits that both amphetamine and methamphetamine are active-they just have different activity levels. Applicants strongly reject the implied notion that to be enabled compounds must have the "same" level of activity. Clearly Applicant's compounds can have varying levels of activity and Applicant has not asserted otherwise. In addition, amphetamine and methamphetamine are not alpha-2-ligands—they are part of a group of compounds that act by increasing levels of for example, serotonin on receptors other than alpha-2-ligands.

In compliance with 112 Applicant asserts that his claims are enabled as amply supported in the specification. First, it is well known that alpha-2-delta ligands are associated with pharmacological activity as stated in the instant specification paragraphs [0003] to [0006].

Second, Applicant submits that in compliance with the above-described case law he has stated that the compounds are effective for their intended use in the specification (e.g., see the instant U.S. published application paragraph [0116]; and paragraphs [0118] through [0131].

Applicant submits that he has fully enabled the use of the instantly claimed compounds. The instant U.S. published application in paragraphs [0207] and [0209], describe appropriate dosage levels. Treatment methods are disclosed in the paragraphs [0172]; [0186]; [0189]; [0196]; [0199]; [0201]; [0205]. The specification teaches at paragraphs [0207] and [0208] appropriate dosage levels. Further, the specification teaches (see U.S. published application

paragraph [0116]) test protocols which aid in determining the activity/relative activity of the compounds and thus appropriate dosage levels. In addition, the specification is replete with description of how to formulate the compounds. Applicant submits that this is sufficient to meet the standards of enablement under 35 U.S.C. §112.

The points and concerns raised by the Examiner having been fully addressed. Applicants urge that this application is in condition for allowance, which action is respectfully requested.

Please charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445.

Respectfully submitted,

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